as follows:

--1.(2X amended) A protein [comprising] consisting of a CRAF1 amino acid sequence shown in Figure 1 truncated at the amino terminus by [at least] 323 amino acid residues up to 414 amino acid residues, or a variant thereof wherein the variant comprises a conservative amino acid substitution, capable of inhibiting CD40-mediated cell activation.--

REMARKS

Claims 1-20 were pending. The Examiner withdrew claims 5-20 from further consideration. Applicants have canceled claim 2 without prejudice. Applicants have amended claim 1 to more particularly point out the presently claimed invention. Support for the amendment may be found in Figure 1 and inter alia in the specification, for example on page 8, lines 3-8. Support for "conservative amino acid substitution" may be found on page 9 in Table 1 of the subject specification. Applicants have amended the specification to include the appropriate Sequence ID Number as requested by the Examiner. Applicants maintain that these amendments raise no issue of new matter. Thus, claims 1, 3 and 4 are pending.

Election/Restriction

The Examiner stated that applicant's election with traverse of Group I, claims 1-4 in Paper No. 11 is acknowledged. The Examiner stated that the traversal is on ground(s) that the process of Group II cannot be practiced with another materially different product, as now amended. The Examiner did not find this persuasive because, as made of record in the Restriction of February 28, 1998, the inventions can allegedly be shown to be

distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product, or (2) the product as claimed can be used in a materially different process of using that product (MPEP §806.05(h)). The Examiner stated that in the instant case, the polypeptide of Group I may be used in screening assays or to generate antibodies. The Examiner stated that the requirement is still deemed proper and is therefore made final. The Examiner withdrew claims 5-20 from further consideration and stated that claims 1-4 are under consideration in the application.

In response, applicants acknowledge that the Examiner withdrew claims 5-20 from consideration.

Specification

The Examiner objected to the disclosure because the specification at page 22 contains a sequence disclosure without it's corresponding SEQ ID No. The Examiner required appropriate correction.

In response, applicants have amended the disclosure to include the SEQ ID NO where appropriate on page 22. In view of this amendment, applicants request that the Examiner reconsider and withdraw this objection in view of the amendment.

Rejection Under 35 U.S.C. §112, second paragraph

On page 3 of the August 18, 1998 Office Action, the Examiner rejected claims 1-4 as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner stated that the claims are indefinite in that they

only describe the protein of interest by an arbitrary name. The Examiner stated that while the name itself may have some notion of the activity and function of the protein, there is nothing in the claims which distinctly and definitely describes or points out the protein. The Examiner stated that others in the field may isolate the same CRAF1 protein and give such an entirely different name. The Examiner stated that applicant should particularly point out and distinctly claim the CRAF1 protein by claiming characteristics associated with the protein. The Examiner stated that claiming biochemical molecules by a particular name given to the protein by various workers in the field fails to distinctly point out what the protein is. The Examiner also noted that the instant recitation of an apparently truncated protein by the open language "protein comprising CRAF1 truncated..." is confusing because it isn't clear if more than the truncated protein is contemplated.

The Examiner also stated that the phrase "CD40 mediated cell activation" found in claim 1 is vague and indefinite because the metes and bounds of what is including and definitive of "activation" cannot be determined. The Examiner stated that neither the claims nor the specification provide a clear definition of what parameters determine or are definitive of cell activation. The Examiner also stated that dependent claims 2-4 do not clarify the above indefiniteness.

In response, applicants respectfully traverse the rejection of claims 1-4 under 35 U.S.C. §112, second paragraph. Without conceding the correctness of the Examiner's position, applicants have amended claim 1 hereinabove and maintain that the amendment raises no issue of new matter. Applicants have amended the claim to recite "consisting of" in order to address and obviate the Examiner's objection to the language "comprising." Applicants have also amended claim 1 to include a reference to the amino acid sequence of CRAF1 shown in Figure 1 of the present

application. Applicants maintain that the presently claimed invention is particularly pointed out in the language of claim 1. Applicants maintain that the present invention is distinctly claimed and request the Examiner to reconsider and withdraw this ground of rejection.

As to the Examiner's concern regarding the phrase "CD40 mediated cell activation," applicants maintain that one of skill in the art would know how to determine cell "activation" and to illustrate this point, applicants have attached hereto as **Exhibit 1** a reference which indicates that one of skill would know the metes and bounds of CD40 mediated cell activation prior to the effective filing date of March 11, 1996. The reference, Potocnik et al., (1990) "Expression of Activation Antigens on T Cells in Rheumatoid Arthritis Patients" Scand. J. Immunol. 31:213-224, examined both normal and rheumatoid patient synovial tissue for CD40 expression by the monoclonal antibody B-E10. CD40 triggering of B cells was known prior to the effective filing date of the present application. CD23 upregulation is one marker of B cell activation.

In addition, applicants draw the Examiner's attention to page 24, beginning at line 24 of the present specification. Therein, applicants describe the upregulation of CD23 as an indicator of cell activation in response to CD40 triggering. In this working example, a Ramos cell line transfected with the C26 clone had diminshed capacity to upregulate CD23 in response to CD40L-CD40 signals. Thus, the line transfected with the C26 clone demonstrated inhibition of CD40 mediated cell activation.

Furthermore, applicants draw the Examiner's attention to Hu et al. J. Biol. Chem., 269(48):30069. This reference is dated December 2, 1994 on its face and clearly indicates that one of skill would have understood the metes and bounds of the phrase "CD40 mediated cell activation." In the introductory paragraph,

Hu et al. disclose that "CD40 activation is critical for B-cell proliferation, immunoglobulin class switching, and rescue of germinal center B-cells from apoptosis following somatic mutation." Clearly, there are numerous markers of CD40 mediated cell activation which would have been known to one of skill in the art which mark the activation of a cell due to CD40 signalling.

In view of the above remarks and amendments, applicants respectfully request the Examiner reconsider and withdraw this ground of rejection.

Rejection Under 35 U.S.C. §112, first paragraph - Written Description

The Examiner rejected claims 1-4 as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Examiner stated that claim one (and therefore dependent claims 2-4) has been amended to recite truncation of "at least 323 amino acid residues up to 414 amino acid residues" for which the specification fails to provide support. The Examiner stated that the specification provides support for truncations of about 323 amino acids to about 414 amino acids. The Examiner further asserted that nowhere is it set forth that the truncation must be at least 323 amino acids. The Examiner stated that the original language indicates that the exact value may vary. Similarly, the Examiner stated, the specification provides support for truncations of about 414 amino acids, not exactly 414 amino acids, the original specification and claim language indicates that the truncation may be slightly more than 414 amino acids, but must be about 414 amino acids. Thus, the Examiner

stated, the instant amendment alters the claimed invention in scope from that originally disclosed. The Examiner suggested that in order to distinctly claim the truncation as supported by the original disclosure, without introducing indefiniteness, the claims may be amended to recite amino terminus truncations of 323 amino acids to 414 amino acids residues which s contemplated by the original specification, or more ideally, to recite the amino acid range of the truncated protein as disclosed on page 5 and in Figure 2.

In response, applicants respectfully traverse the rejection of claims 1-4 under 35 U.S.C. §112, first paragraph. Without conceding the correctness of the Examiner's position, applicants have amended claim 1 to more particularly point out the presently claimed invention. Applicants have removed the phrase "at least" from claim 1. The presently claimed invention is directed to a protein consisting of a CRAF1 amino acid sequence shown in Figure 1 truncated at the amino terminus by 323 amino acid residues up to 414 amino acid residues, or a variant thereof wherein the variant comprises a conservative amino acid substitution, capable of inhibiting CD40-mediated cell activation. Applicants point out that the sequence claimed in claim 1 is supported by the subject specification, specifically, Figure 1. Also, applicants have described such proteins as presently claimed in the subject specification on page 8, line 3 to page 12, line 14 and have provided examples of such a protein in Figures, 1, 2A and 3 and on pages 5, lines 3-13 and page 5, line 31 to page 6, line 28. The specification provides a full written description of the claimed proteins and includes several working examples. See, for example, the C26 clone shown in Figure 3. Thus, applicants maintain that the specification provides sufficient written description of the presently claimed invention. In view of the above remarks and amendments, applicants respectfully request the Examiner to reconsider and withdraw this ground of rejection.

Rejection Under 35 U.S.C. §112, first paragraph - Enablement

The Examiner rejected claims 1-4 under 35 U.S.C. §112, first paragraph as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected to make and/or use the invention. The Examiner stated that the specification is not enabling for the invention as broadly claimed. The Examiner stated that the specification is not enabling for any variant of truncated CRAF1 protein or truncated CRAF1 proteins which inhibit any CD40 mediated cell activation.

The Examiner stated that the factors to be considered have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex Parte Forman*, (230 USPQ 546 (Bd Pat. App. & Int. 1986)).

The Examiner stated that the instant specification maps the regions responsible for binding to CD40 to the TRAF domain while the function of the other domains present in CRAF1 remains speculative. Further, the Examiner stated that the specification discloses that truncated CRAF1 proteins retaining the C-terminal TRAF domain (TRAF-C domain) defined by amino acid residues 415-567 of SEQ ID NO: 1 or 2 function as individual CD40 binding units which may have inhibitory properties. The Examiner stated that the specification further discloses that one specific truncated protein, C26, which consists of amino acid residues 324-567, serves as a dominant negative protein, inhibiting CD40 cell mediated CD23 upregulation.

The Examiner stated that thus, the disclosure of the instant specification supplies sufficient objective evidence and guidance to make it predictable that amino truncated CRAF1 proteins retaining TRAF-C domain would bind to CD40 with properties similar to the C26 example. However, the Examiner stated, the specification does provide sufficient guidance and objective evidence that any variant of a CRAF1 truncated protein would reasonably be expected to retain CD40 binding properties and inhibitory activity. The Examiner stated that the specification contemplates variants including amino acid substitutions, deletions, or insertions, or other chemical modifications of substituents (pages 8-11). However, the Examiner stated, the specification fails to provide sufficient guidance (with the exception of conservative substitutions as recited in claim 2) directing one of skill to determine where within the truncated protein the modifications are acceptable and what types of modifications are predicted to result in similar binding and inhibitory activities. The Examiner stated that the specification discloses only that the TRAF-C domain is necessary, but supplies insufficient information regarding what sequences within this domain may be modified and still predictably result in similar activity. The Examiner stated that the amino acid sequence of a protein determines its structural and functional properties, and predictability of which amino acids can be substituted or modified within a protein's sequence and still result in similar activity is extremely complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's structure and function from mere sequence data are limited. The Examiner stated that since detailed information regarding the structural and functional requirements of this protein are lacking, it is unpredictable as to which amino acid substitutions, if any, meet the limitations of the claim. The Examiner stated that furthermore, while recombinant techniques are available, it is not routine in the art to screen large numbers of substituted proteins where the

expectation of obtaining similar activity is unpredictable based on the instant disclosure. Therefore, the Examiner stated, one of ordinary skill would require guidance, such as information regarding the extent of substitution and the location and the specific amino acid changes which would result in the preservation of the stated activity. The Examiner stated that therefore, it would require undue experimentation by one of skill in the art to practice the invention as claimed without further guidance from the instant specification.

The Examiner stated that additionally, as discussed supra, the phrase "CD40 mediated cell activation" is vague and indefinite because it is not clear what measurable properties of "activation" correlate with CD40 mediated cell "activation," nor is it clear when a cell is determined to be "activated." The Examiner stated that the specification provides guidance for the determination of inhibition by detecting CD40 mediated CD23 upregulation. The Examiner stated that there is insufficient guidance or objective evidence to support the correlation of any other measurable "properties" and cell "activation." The Examiner stated that the specification contemplates that "activation" may include any and all intracellular signalling, immune responses, allergic responses, apoptosis (pages 14-18), yet there is no guidance provided teaching the accurate determination and measurement of "activation" of these processes and their inhibition. The Examiner stated that absent further guidance it would require undue experimentation to practice the instant invention and to predictably identify inhibitory truncated proteins as broadly claimed.

In response, applicants respectfully traverse the rejection of claims 1-4 under 35 U.S.C. §112, first paragraph and maintain that the specification fully enables the presently claimed invention. Guidance as to where within the truncated protein the variation from the CRAF1 sequence may be found in the

specification on page 8, beginning at line 19. Conservative substitutions are fully described and enabled. Table 1, on page 9 of the specification also provides specific guidance as to which substitutions would be considered conservative. Applicants maintain that the specification and the references included therein (i.e., Dayhoff in the Atlas of Protein Sequence and Structure (1988) as recited on page 9 of the specification) provides a fully enabling disclosure for the presently claimed invention.

As to the Examiner's comments regarding "CD40 mediated cell activation," applicants respectfully traverse. Applicants point out that the present invention is directed to a protein consisting of a CRAF1 amino acid sequence shown in Figure 1 truncated at the amino terminus by 323 amino acid residues up to 414 amino acid residues, or a variant thereof wherein the variant comprises a conservative amino acid substitution, capable of inhibiting CD40-mediated cell activation. Applicants maintain that the specification fully enables CD40 mediated cell activation and that one of skill in the art would know how to determine CD40 mediated cell activation.

First, the specification provides a working example of determining CD40 mediated cell activation. The specification shows the determination of the level of CD23 expression and discloses that a lack of upregulation of CD23 in a Ramos cell line indicates an inhibition of CD40-mediated cell activation. Thus, the cell activation was measured by determining the level of CD23 upregulation. This is a marker that one can use to determine CD40-mediated cell activation.

Second, applicants maintain that one of skill in the art would know other markers of CD40-mediated cell activation and would know how to measure them. See for example, Exhibit 1 attached hereto. Applicants refer the Examiner to the discussion of

Exhibit 1 hereinabove and maintain that Potocnik et al. (1990) disclose differences in cell surface marker expression between T cells from normal individuals and T cells recovered from inflamed joints of rheumatoid arthritis (RA) patients (activated T cells). Potocnik et al. found the molecules B-C5, CD39, CD40, CD45 RO, CD54, CD76 and potentially 1D11 to be substantially upregulated on T cells from various body compartments in RA patients. Clearly, as of 1990, one of skill in the art would have known of these activation markers and how to measure them.

In view of the amendments and remarks, applicants respectfully request the Examiner to reconsider and withdraw this ground of rejection.

Rejection Under 35 U.S.C. §102(b)

The Examiner rejected claims 1-4 under 35 U.S.C. §102(b) as being anticipated by Sato et al. (FEBS Lett. 358:113-118, Jan. 23, 1995) or Hu et al. (J. Biol. Chem. 269:30069-30072, Dec. 1994 - IDS) or Cheng et al. (Science 267:11494-1498, March 10, 1995 - IDS).

The Examiner stated that Sato et al. teach a truncated clone of CAP-1 which encodes little more than the C-terminal region of CAP-1, between amino acid residues 384-540 sufficient to mediate binding to CD40. The Examiner stated that Sato et al. are silent regarding the inhibitory properties of the truncated protein, however, CAP1 is identical to the instant CRAF1, and the capability of the truncated protein to inhibit CD40 mediated activation events such as CD23 would be an inherent property of the truncated product.

The Examiner further stated that Hu et al. teach the same CAP1, LAP1, CRAF1 protein, termed CD40bp and a truncated version of only the C-terminal half, from amino acid residue 297-the end,

which binds to CD40. The Examiner stated that like Sato et al., Hu et al. is silent regarding the inhibitory properties of the truncated protein, however, such properties would be inherent to the product.

The Examiner stated that Cheng et al. teach that truncated CRAF1, clone C26, identical to the instant product, inhibits CD40-mediated up-regulation of CD23.

The Examiner noted that the proteins designated CRAF1, CAP1 (Sato et al.), CD40bp (Hu et al.), as well as LAP1 (Mosialos et al. - IDS) refer to the same protein, as acknowledged in the instant specification on page 2 and as exemplified by the enclosed sequence data.

The Examiner stated that thus, each of Sato et al., Hu et al., and Cheng et al. teach truncated CRAF1 protein products as claimed which would inherently possess the same inhibitory properties.

In response, applicants respectfully traverse the rejection of claims 1-4 under 35 U.S.C. §102(b) over Sato et al., Hu et al. or Cheng et al. Applicants maintain that none of these references anticipate the presently claimed invention.

First, applicants maintain that Cheng et al. is not a proper reference under 35 U.S.C. §102(b). The present application claims the priority of U.S. Provisional Application No. 60/013,199, filed March 11, 1996. As to the Cheng et al. reference, the journal *Science*, volume 267 dated March 10, 1995, was placed into the U.S. Mail on March 10, 1995. Applicants attach hereto as **Exhibit 2** a letter from Ms. Helen Williams of the American Association for the Advancement of Science indicating that March 10, 1995 issue date of *Science* was in fact the date of mailing. Thus, subscribers to the journal *Science*

would not have been in possession of the journal dated March 10, 1995 until, at the earliest, March 11, 1995. Furthermore, March 11, 1995 is not more than one year prior to March 11, 1996. Therefore, applicants maintain that Cheng et al. is not a proper reference under 35 U.S.C. §102(b). Accordingly, applicants respectfully request the Examiner to reconsider and withdraw this ground of rejection based upon Cheng et al.

Furthermore, if the Examiner were to reject claims 1, 3 and 4 under 35 U.S.C. §102(a) over the Cheng et al. reference, applicants maintain that the Cheng et al. reference is not a publication "by others" as required under 35 U.S.C. §102(a). If the Examiner rejects the pending claims under 35 U.S.C. §102(a) in view of Cheng et al., applicants are prepared to submit a Declaration Under 35 U.S.C. §1.132 as evidence that David Hong (the only author of Cheng et al. who is not named as an inventor of the present application) did not contribute to the conception of the claimed invention.

Applicants maintain that neither Sato et al. nor Hu et al. anticipate the presently claimed invention. In order for a reference to anticipate the claimed invention, it must disclose every element of the claimed invention. Sato et al. do not disclose the truncated protein as presently claimed. The Examiner stated that "CAP1 is identical to the instant CRAF1" on page 8 of the August 18, 1998 Office Action. Applicants respectfully disagree. Applicants point out that the CAP1 sequence disclosed by Sato et al. is a different length than the CRAF1 sequence shown in Figure 1 of the present application. Furthermore, there are numerous amino acid sequence differences between the two proteins. Finally, Sato et al. do not disclose a truncated protein as presently claimed. It is clear that the truncated protein as presently claimed is different than the CAP1 sequence disclosed in Sato et al. Since the proteins are different on their face (see Figure 2 of Sato et al. as compared

with Figure 1 of the present specification), truncated versions of each protein would also be different. The inherency argument presented by the Examiner does not hold true. Clearly, different proteins will have different inherent characteristics. Therefore, Sato et al. do not anticipate the presently claimed invention.

Hu et al. do not anticipate the presently claimed invention. Hu et al. do not disclose the truncated protein presently claimed. Figure 4, panel A of Hu et al. discloses an amino acid sequence of a protein termed CD40bp. Hu et al. do not disclose a protein consisting of a CRAF1 amino acid sequence shown in Figure 1 of the subject specification which is truncated at the amino terminus by 323 amino acid residues up to 414 amino acid residues, or a variant thereof wherein the variant comprises a conservative amino acid substitution, capable of inhibiting CD40-mediated cell activation. The Examiner stated that Hu et al. teaches "truncated version of only the C-terminal half, from amino acid 297-the end...." Applicants disagree with the Examiner's summary of the Hu et al. disclosure and maintain that Hu et al. do not teach a truncated version of CD40bp. Hu et al. merely disclose various characteristics of the full-length protein (see column 1, page 30072) and do not disclose a truncated protein. However, Hu et al. do mention a truncated TRAF2 protein, which is missing the RING finger domain, in the first sentence of the last paragraph of the reference. This is not a disclosure of a truncated protein as presently claimed. Applicants also point out that the Hu et al. reference does not disclose such a truncated protein as presently claimed which is capable of inhibiting CD40-mediated cell activation.

Thus, applicants maintain that the presently claimed invention is not anticipated by either Sato et al. or Hu et al. Furthermore, applicants maintain that Cheng et al. is not a proper reference under 35 U.S.C. §102(b). In view of the above

amendments and discussion, applicants respectfully request that the Examiner reconsider and withdraw the outstanding grounds for rejection and earnestly solicit the allowance of pending claims 1, 3 and 4.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the $435.00 extension of time fee, is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

John P. White
Registration No. 28,678
Attorney for Applicants
Cooper & Dunham LLP
1185 Avenue of the Americas
New York, New York 10036
(212) 278-0400

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:
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2/18/99
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